REMARKS

Claims 19, 21-28, 63-78, 90, 92-99, 100-103, and 105-114 are pending upon entry of the above amendments. Claims 20, 80-83, 91, 104, and 115-116 have been canceled without prejudice. Applicant reserves the right to prosecute the subject matter of any canceled claims in one or more continuation, continuation-in-part, or divisional applications. Claims 19, 21-23, 25-26, 28, 63-78, 90, 92-94, 96-97, 99, 103, 105-107, 109-110, and 112-114 have been amended to clarify the invention. Support for the amended claims may be found in the specification. Specifically, examples of support for claims 19, 63, 65, 69, 71, 73, 75, and 103 can be found on page 5, line 15 to page 6, line 7 of the instant specification. Examples of support for claims 25, 26, 65, 66, 96, 97, 109, and 110 can be found on page 9, line 14 to page 10, line 9 of the instant specification. Examples of support for claims 64, 67, 68, 74, 76, 90, and 103 can be found on page 10, lines 10-12 and on page 11, lines 3-5 of the instant specification. Examples of support for claims 75 and 77 can be found on page 7, lines 13-20 and page 11, lines 12-17 of the instant specification. Examples of support for claim 113 can be found on page 14, line 22 to page 15, line 2 and page 18, lines 7-11 of the instant specification. Thus, the amended claims are fully supported by the instant specification and no new matter has been introduced.

Claims 25, 65, 96, and 109 have been amended to recite "phosphate-modified nucleotides". Applicant notes that, as agreed upon with Examiner at the interview conducted on May 29, 2003, "phosphate-modified nucleotides" is intended to encompass not only nucleotides with changes to the phosphate group, but also nucleotides in which the phosphate group has been replaced with a different group.

A. Rejections Under 35 U.S.C. § 112

1. The Rejection Under 35 U.S.C. § 112, first paragraph

Claims 19-28, 63-78, 80-83, and 90-116 are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The Examiner contends that the phrase "non-traditional nucleotides" (claims 25, 26, 65, 66, 96, 97, 109, and 110) is new matter. Without in any way conceding that "non-traditional nucleotides" is new matter and for the sole purpose of expediting prosecution of this application, Applicant has amended the claims such that the phrase "non-traditional

nucleotides" is no longer recited. Instead, the claims have been amended to recite "phosphate-modified nucleotides" pursuant to the Examiner's suggestion in the interview conducted May 29, 2003.

The Examiner contends that the phrase "saponin immunostimulatory adjuvant" (claims 63, 65, 69, 71, 73, 75, and 103) is new matter. Without in any way conceding that an "saponin immunostimulatory adjuvant" is new matter and for the sole purpose of expediting prosecution of this application, Applicant has amended the claims such that the phrase "saponin immunostimulatory adjuvant" is no longer recited thereby rendering the rejection moot. Instead, the claims have been amended to recite "a saponin possessing immune adjuvant activity, wherein the saponin is derived from *Quillaja saponaria*" which is supported in the specification on page 5, lines 15-17 and on page 10, lines 10-21.

The Examiner contends that the phrase "antigen to which an immune response is desired" (claims 64, 67, 68, 74, 76, 90, and 103) encompasses a scope of antigens that does not have support in the specification as originally filed. Applicant respectfully disagrees. The specification, as the Examiner points out, does list organisms from which antigens for use in the methods of the invention can be derived (page 14, lines 17-22 of the instant specification). However, these are *examples* of the types of antigens which can be used in the methods of the invention - - nowhere in the specification is this characterized as a complete list of all possible antigens. In fact the specification discloses that the methods of the present invention can be used to enhance the immune response to *any* antigen (see page 13, lines 19-21 of the instant specification). Any antigen to which an immune response is desired may be used in the methods of the invention. Each skilled artisan can decide for themselves what antigen they desire to obtain an immune response against. However, without in any way conceding that an "antigen to which an immune response is desired" is not supported in the specification, for the sole purpose of expediting prosecution of this application, and since it will be understood that the "antigen" in the last line of the claim is one for which the immune response is induced (by reference to the preamble of the claim), Applicant has amended claims 64, 67, 68, 74, 76, 90, and 103 such that the phrase "antigen to which an immune response is desired" is no longer recited, thereby rendering the rejection moot.

The Examiner contends that the phrase "an individual or test system to which a nucleic acid encoding the antigen is administered" (claims 64, 67, 68, 70, 72, 74, 76, 80, 90, and 103) is new matter. Applicant has amended claims 64, 67, 68, 70, 72, 74, 76, 80, 90,

and 103 to delete the phrase "test system". Applicant respectfully disagrees that the phrase "an individual to which a nucleic acid encoding the antigen is administered" is new matter. The specification does support the administration of a nucleic acid encoding an antigen. The immune response as recited in the claims is the immune response that is directed toward an antigen. While the specification discloses various examples of an "antigen" as a protein, a peptide, a polysaccharide, a lipid, a glycolipid, a phospholipid, or "a nucleic acid encoding the antigenic protein or peptide of interest" (see page 14, line 22 to page 15, line 1of the instant specification), it is clear to one of skill in the art that the nucleic acid *encodes* the antigen against which the immune response is desired rather than *being* the target of the immune response directly. It is also evident from the specification that referring to the nucleic acid as an example of an "antigen" was merely a short-hand reference so that "nucleic acid encoding an antigen" need not be repeated in every context where "antigen" was used in the specification. By describing the encoded protein or peptide as the *antigenic* protein or peptide of interest, one of skill in the art would understand that it is the encoded product which serves as an antigen and thus, the immune response is directed against it rather than the nucleic acid that encodes it.

The Examiner contends that the phrase "non-traditional saponin" (claims 75 and 77) is new matter. Without in any way conceding that a "non-traditional saponin" is new matter and for the sole purpose of expediting prosecution of this application, Applicant has amended the claims such that the phrase "non-traditional saponin" is no longer recited, thereby rendering the rejection moot. Instead, amended claims 75 and 77 recite "chemically modified saponin" which is supported in the specification on page 7, lines 16-20 and on page 11, lines 12-17.

The Examiner contends that the phrase "an effective amount" (claim 90) is new matter. Applicant respectfully disagrees. Claim 90 has been amended such that the amount of immune adjuvant composition administered is effective to increase the immune response. Clearly, the specification discloses the use of an immune adjuvant to increase an immune response. For example, the term "immune adjuvant" is defined in the specification as a compound having just such an activity (see page 10, lines 10-12 of the instant specification). Moreover, the specification discloses examples of assays that can be used to determine if an immune response has been induced (see page 6, line 8 to page 7, line 7 of the instant specification). According to applicable case law, "ipsis verbis disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the

disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question." Fujikawa v. Wattanasin, 93 F.3d 1559, 39 USPQ 2d 1895, 1904 (Fed. Cir. 1996).

The Examiner contends that the phrase "wherein the nucleic acid encoding the antigen is administered to the individual or test system within 0-2 days of the administration of the immune adjuvant composition" (claim 113) is new matter. Applicant has amended claim 113 to delete the phrase "test system" and to replace "0-2 days" with "within 2 days". Applicant respectfully disagrees that the phrase (as amended) "wherein the nucleic acid molecule comprising a nucleotide sequence encoding the antigen is administered to the individual within 2 days of said administering of the immune adjuvant composition" is new matter. The specification contemplates administering a saponin, an oligonucleotide, and an antigen as a mixture or at separate times (*e.g.*, on page 18, lines 7-11 of the instant specification). Administration of an "antigen" as that term is used in the specification (see page 15, lines 1-2 of the instant specification) encompasses administration of a nucleic acid encoding an antigen. Thus, the specification clearly discloses the administration of a saponin, immunostimulatory oligonucleotide, and a nucleic acid molecule comprising a nucleotide sequence encoding the antigen together or separately.

The Examiner contends that claims 115 and 116 are new matter. Without in any way conceding that the subject matter of claims 115 and 116 is new matter, for the sole purpose of expediting prosecution of this application, and with fully reserving our rights to prosecute this subject matter in a subsequent patent application, Applicant has canceled claims 115 and 116 thereby rendering the rejection moot.

Claims 19-28, 63-78, 80-83, and 90-116 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner admits that the specification is enabled for a method of inducing an immune response in an individual comprising administering i) a vector comprising a nucleic acid encoding an antigen and ii) a nucleic acid comprising at least one unmethylated CpG. However, the Examiner contends that merely administering an immune adjuvant without a nucleic acid encoding an antigen is not enabled (see page 7, lines 6-14 of the Office Action mailed January 31, 2003).

Applicant respectfully disagrees. Applicant notes that claims 80-83, 91, and 115-116 have been canceled and thus the rejection is moot with respect to these claims. With respect to claims 19-28 and 63, 65, 66, 69, 71, 73, 75, 77, 78, and 103-112, these are composition claims. Even assuming *arguendo* that the Examiner's contention that

administration of an immune adjuvant alone without a nucleic acid encoding an antigen is not enabled, Applicant points out that the claimed immune adjuvant *compositions* are enabled, based on use as intermediates. The claimed compositions can be used as intermediates to which an antigen can be added. As such the compositions are enabled. While the method claims (claims 64, 67-68, 70, 72, 74, 76, 90, 92-102, and 113-114) do not require a step wherein the nucleic acid molecule comprising a nucleotide sequence encoding an antigen is administered, the claims do specify that the individual is one to which the nucleic acid encoding an antigen is administered (*e.g.*, within 2 days before or after administration of the immune adjuvant). That is, the individual in which the immune response is induced by the claimed method is further defined by the condition that he or she is administered a nucleic acid molecule comprising a nucleotide sequence encoding an antigen. By analogy, in method of treatment claims for a disorder, Applicants are not required to add a step to the claim where the subject is first given the disorder before treatment. Rather, those subjects having the disorder are the population of individuals to which the treatment is administered. Applicant contends that the present situation is comparable. The population of individuals to which the methods of claims 64, 67-68, 70, 72, 74, 76, 90, 92-102, and 113-114 can be used to induce an immune response are described as those who are administered an antigen(before, concurrently with, or after the administration of the saponin and immunostimulatory oligonucleotide); thus the claims are enabled.

2. <u>The Rejections Under 35 U.S.C. § 112, second paragraph</u>

Claims 19-28, 63-78, 80-83, and 90-116 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Applicant respectfully disagrees.

According to applicable case law, the requirement of 35 U.S.C. § 112, second paragraph, means that the claims must have a clear and definite meaning when construed in the light of the complete patent document. <u>Standard Oil Co. v. American Cyanamide Co.</u>, 774 F.2d 448, 227 U.S.P.Q. 293 (C.A.F.C. 1985). The test of definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. <u>Orthokinetic Inc. v. Safety Travel Chairs, Inc.</u>, 806 F.2d 1565, 1 U.S.P.Q.2d 1081 (C.A.F.C. 1986). In the present situation, the claims are definite when considering the disclosure of the instant specification for the reasons stated below.

The Examiner contends that the phrase "immunostimulatory oligonucleotide having an unmethylated CpG" (claims 19, 24, 25, 27, 63, 65, 69, 71, 73, 75, 95, 96, 98, 103, 108, 109, and 111) is indefinite because the metes and bounds of the oligonucleotides excluded from the claims cannot be determined. The Examiner agrees that upon reading the specification it is clear that the immunostimulatory oligonucleotide can be any length and have any sequence comprising an unmethylated CpG (page 9, lines 8-14 of the Office Action mailed January 31, 2003). It is unclear to Applicant how such a clear term can be indefinite. The term is meant to encompass all such oligonucleotides - excluding none.

The Examiner contends that the metes and bounds of the phrase "non-traditional nucleotides" (claims 25, 26, 65, 66, 96, 97, 109, and 110) is indefinite. Applicant has amended the claims to recite that the immunostimulatory oligonucleotide comprises one or more "phosphate-modified" nucleotides pursuant to the Examiner's suggestion in the interview conducted May 29, 2003. The term "phosphate-modified nucleotides", as agreed upon by Applicant and the Examiner at the interview, encompasses not only nucleotides with changes to the phosphate group, but also nucleotides in which the phosphate group has been replaced with a different group. The specification clearly discloses examples of such types of modifications that the immunostimulatory oligonucleotides may have as well as directs one of skill in the art to relevant references which disclose well known methods of making oligonucleotides with such modifications (*e.g.* page 9, line 14 to page 10, line 9 of the instant specification).

The Examiner contends that the metes and bounds of the phrase "antigen to which an immune response is desired" (claims 64, 67, 68, 74, 76, 90, and 103) cannot be determined. Applicant has amended these claims to delete the phrase and to clearly point out that the antigen to which an immune response is induced is the antigen encoded by the administered nucleic acid molecule.

The Examiner contends that the metes and bounds of the phrase "saponin immunostimulatory adjuvant" (claims 63, 65, 69, 71, 73, 75, and 103) cannot be determined. Applicant has amended the claims to recite a "saponin possessing immunostimulatory adjuvant activity wherein the saponin is derived from *Quillaja saponaria*". Applicant points out that the saponins used in the compositions and methods of the invention are specified as having a clearly understood property - - namely an immunostimulatory adjuvant activity. Moreover, it is within the common knowledge and skill in the art to determine if a particular *Quillaja saponaria* saponin possess

immunostimulatory adjuvant activity (*e.g.*, using assays described in the instant specification on page 6, line 8 to page 7, line 7).

The Examiner contends that the preambles of claims 64, 67, 68, 70, 72, 74, 76, and 90 are unclear. The Examiner contends that it is unclear if the immune response is "desired" or "increasing". Applicant has amended the claims such that it is clear that the immune response is "induced", as discussed with the Examiner at the interview of May 29, 2003. The Examiner further contends that the claims do not require the administration of a nucleic acid encoding an antigen and, as such, the phrase "to which a nucleic acid encoding the antigen is administered" is unclear. Applicant asserts that the phrase "to which a nucleic acid encoding the antigen is administered" further describes the individual in whom an immune response is induced. While claims 64, 67, 68, 70, 72, 74, 76, and 90 do not require a step wherein the nucleic acid molecule comprising a nucleotide sequence encoding an antigen is administered, the claims do specify that the individual is one to which antigen is administered (*e.g.*, within 2 days before or after administration of the immune adjuvant). As such, the phrase "to which a nucleic acid encoding the antigen is administered" is a characteristic of the individual in whom an immune response is induced by the methods of the invention rather than a method step required in the claim. The Examiner states that the phase "nucleic acid" refers to one nucleotide and as such cannot encode an antigen. Applicant respectfully disagrees, and notes the claims have been amended to recite "a nucleic acid molecule comprising a nucleotide sequence encoding the antigen". The Examiner further believes it is unclear whether the phrase "to which a nucleic acid...is administered" refers to just the test system or the either the individual or the test system. Applicant notes that the phrase "test system" has been deleted from claims 64, 67, 68, 70, 72, 74, 76, and 90, thus it is clear that the phrase "to which a nucleic acid...is administered" refers to the individual.

The Examiner contends that the metes and bounds of the phrase "non-traditional saponin" (claims 75 and 77) is indefinite. Applicant has amended the claims to recite a chemically modified saponin. One of skill in the art would understand that the term "chemically modified" as used in the above-mentioned claims and in the present specification to be a chemical modification that is a covalent modification that alters the structure of the saponin. Chemically modified saponins are known in the art and the specification gives examples of some chemical modifications (*e.g.*, page 7, lines 13-20 of the instant specification), all of which are covalent alterations. Stedman's Medical

Dictionary 27th edition (2000, Lippincott Williams & Wilkens:New York, page 1123 submitted herewith as Exhibit A) defines a chemical modification as an alteration in structure of a molecule...by chemical means; often by the covalent addition of some reagent. It is clear that one of skill in the art would clearly understand the term to mean as defined above.

The Examiner contends that claim 80 is indefinite. Applicant has canceled claim 80 and, as such, the rejection is moot.

The Examiner contends that claim 90 is unclear because the phrase "a nucleic acid" can refer to the DNA vaccine vector or some other nucleic acid. Applicant notes that claim 90 has been amended and no longer recites the phrase "a nucleic acid". Amended claim 90 now refers to a nucleic acid molecule comprising a nucleotide sequence encoding the antigen. Such a nucleic acid molecule encompasses both DNA vaccine vectors as well as other nucleic acid molecules that encode an antigen.

The Examiner contends that claim 90 indefinite because it does not clearly refer back to the immune adjuvant composition of claim 19. Applicant has amended the claim as per the Examiner's suggestion.

With respect to claim 90, the Examiner contends that the metes and bounds of "an effective amount" of the immune adjuvant cannot be determined. Applicant has amended the claim to recite "an amount of immune adjuvant effective to induce the immune response". It is clear that the amount of immune adjuvant that can induce an immune response to the antigen encoded by the administered nucleic acid molecule is an "effective amount". One of skill in the art could determine the appropriate amount of immune adjuvant to administer using only routine experimentation. The phrase "an effective amount" is indefinite when the claim fails to state the function which is to be achieved. Application of Charles Andrew Watson 517 F.2d 465 (Pat. Off. Bd. App. 1975). Claim 90 does recite a function - - induction of an immune response - - so it is therefore not indefinite.

The Examiner contends that the phrase "operatively linked to a promoter" in claim 103 is unclear because which nucleotide sequence it is referring to is ambiguous. The Examiner has suggested that if the phrase "operatively linked to a promoter" is defining the structure of the nucleotide sequence that encodes the antigen (in section (c) of claim 103), then it should be recited in the same section of the claim (*i.e.*, section (c) of claim 103).

While Applicant disagrees with the rejection, nevertheless, Applicant has amended the claim to conform with this suggestion.

The Examiner contends that claim 108 is indefinite because it is unclear if the unmethylated CpG dinucleotide is referring to the unmethylated CpG motif of claim 103 or if the unmethylated CpG dinucleotide is in addition to the unmethylated CpG motif. Applicant notes that claim 103 has been amended to recite "an immunostimulatory oligonucleotide comprising at least one unmethylated CpG dinucleotide" rather than "an immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif". Thus, the CpG motif recited in claim 108 comprises the at least one unmethylated CpG dinucleotide of claim 103 and specifies that the motif has more than one unmethylated CpG dinucleotide.

The Examiner contends that claim 113 is indefinite because the nucleic acid is not administered to the individual in claims 64, 67, 68, 70, 72, 74, 76, or 77. Applicant has amended the claims on which claim 113 depends such that the individual in whom an immune response is induced is one to which a nucleic acid molecule encoding antigen is administered. Thus, the individuals of claims 64, 67, 68, 70, 72, 74, or 76 are defined by a common characteristic of being administered a nucleic acid molecule comprising a nucleotide sequence encoding an antigen. As such, claim 113 merely specifies the time period within which the nucleic acid molecule comprising a nucleotide sequence encoding the antigen is administered (*i.e.*, within 2 days before or after administration of the immune adjuvant). Furthermore, the Examiner contends that phrase "the administration" lacks antecedent basis. Applicant has amended the claim to replace "the administration" with "said administering" such that the antecedent basis is now proper.

The Examiner contends that the phrase "within 0-2 days of" is confusing because it is unclear whether the phrase is intended to mean within two days before or two day after administering the immune adjuvant or both. Applicant has amended the claim such that it is clear that the nucleic acid molecule can be administered within either 2 days before or after the immune adjuvant.

The Examiner contends that claim 115 is indefinite. Applicant has canceled claim 115 and, as such, the rejection is moot.

In view of the foregoing, Applicant requests that the Examiner withdraws the rejections under 35 U.S.C. § 112.

B. Rejections Under 35 U.S.C. § 102

1. Rejections Over Urban and Sasaki

Claims 65, 67, 75, 76, and 113-116 are rejected under 35 U.S.C. § 102(e) as being anticipated by United States Patent No. 6,013,258 ("Urban") as supported by Krieg et al., 1998, *Trends in Microbiology* 6:23-26 ("Krieg"). Claims 65, 67, 75-77, and 113-116 are rejected under 35 U.S.C. § 102(e) as being anticipated by United States Patent No. 5,808,024 ("Sasaki") as supported by Krieg. Applicant respectfully disagrees.

Urban discloses delivery of plasmids encoding immunogenic HPV peptides by use of ISCOMS, cage-like structures formed of saponins (Quil A) alone or in combination with cholesterol. The Examiner states that Urban teaches administration of the combination of a plasmid encoding an antigen with saponin or Quil A. The plasmid taught in Urban, according to the Examiner, inherently contains at least one unmethylated CpG dinucleotide. Sasaki discloses *Moraxella* OMP nucleic acids as a vaccine with QS-21 or Quil A as adjuvant or in an ISCOM preparation. The Examiner states that Sasaki teaches administration of the combination of a plasmid encoding an antigen with QS-21. The plasmid taught in Sasaki, according to the Examiner, inherently contains at least one unmethylated CpG dinucleotide. Thus, it is alleged that Urban and Sasaki inherently teach a composition comprising the combination of an immunostimulatory oligonucleotide and the saponin adjuvant QS-21, as well as the administration thereof.

Applicant has amended claims 65, 67, 75-77, and 113-114 clarify the invention (Applicant notes that claims 115-116 have been canceled). The compositions of claims 65, 75, 77 comprise either i) a saponin and an immunostimulatory oligonucleotide (that may or may not be a part of a DNA vaccine vector) comprising phosphate-modified nucleotides or ii) a chemically modified saponin and an immunostimulatory oligonucleotide (that may or may not be a part of a DNA vaccine vector). Applicants contend that neither Urban nor Sasaki disclose any of the above-identified compositions. Previously the claims recited a "non-traditional nucleotide" instead of "phosphate-modified nucleotides" and "non-traditional saponins" instead of "chemically modified saponins". The Examiner contends that the term "non-traditional" can be interpreted broadly such as to encompass naturally occurring alterations in DNA (*e.g.*, nicked DNA) or purified saponins and therefore encompasses the compositions of Urban and Sasaki. Applicant contends that an immunostimulatory comprising phosphate-modified nucleotides does not encompass naturally occurring alterations in DNA. Therefore, the use of plasmids containing

unmethylated CpG dinucleotides as in Urban and Sasaki do not qualify as "phosphate-modified nucleotides". Furthermore, Applicant contends that a chemically modified saponin does not encompass a purified saponin. Therefore, the use of Quil A or QS-21 (purified saponins) as in Urban and Sasaki do not qualify as "chemically modified saponins".

Anticipation under 35 U.S.C. § 102 requires that a single piece of prior art discloses each and every element of the claimed invention, either expressly or inherently. See In re Robertson, 169 F.3d 743, 745, 49 U.S.P.Q. 2d 1949, 1950 (Fed. Cir. 1999). Neither Urban nor Sasaki disclose or suggest an immunostimulatory oligonucleotide comprising phosphate-modified nucleotides or chemically modified saponins therefore each and every claim limitation has not been met.

Applicant notes that the Examiner contends that Quil A is considered a "substantially pure" saponin (see page 15, lines 12-14 of the Office Action mailed January 31, 2003). Applicant respectfully disagrees. The specification at page 5, line 22 to page 6, line 7, teaches that Quil A is "partially purified", as opposed to QS-7, QS-17, QS-18, and QS-21, which are examples of substantially purified saponins.

2. The Rejection Over Agrawal

Claims 19-20, 24-27, 29-32, 65-68, 73-74, 90-91, 95-98, 100-102, and 113-116 are rejected under 35 U.S.C. § 102(e) as being anticipated by United States Patent No. 5,968,909 ("Agrawal"). Applicant respectfully disagrees.

Agrawal teaches a method of *reducing* the immunostimulatory effects of phosphorothioate oligonucleotides used to treat pathogen-mediated disease states and other medical conditions. This is done by altering sequences or structures within the oligonucleotides to produce a *decreased* immune response in an individual to which this oligonucleotide is administered. The oligonucleotides of Agrawal may be combined with amphipathic agents, such as lipids, capable of producing a liposomal formulation of a therapeutic formulation. According to Agrawal, one example of a suitable amphipathic agent to be used in the liposomal formulation is saponin (see column 6, lines 26-29).

Anticipation under 35 U.S.C. § 102 requires that a single piece of prior art discloses each and every element of the claimed invention, either expressly or inherently. See In re Robertson, 169 F.3d 743, 745, 49 U.S.P.Q. 2d 1949, 1950 (Fed. Cir. 1999). In the event that a reference does not explicitly teach all the elements of a claim, anticipation can only

be shown by inherency if the cited reference makes clear that the missing descriptive matter is *necessarily* present in the thing described in the reference and that it would be so recognized by one of ordinary skill in the art. Continental Can Company USA, Inc. v. Monsanto Company, 948 F.2d 1264 (Fed. Cir. 1991) (emphasis added). Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. In re Oelrich, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). Substantial uncertainty regarding the existence of a product in the prior art, *i.e.*, uncertainty as to whether the inherent characteristic *necessarily* flows from the teaching of the prior art reference, is enough to preclude anticipation. W.L. Gore v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983; Bristol-Myers Co. v. USITC, 15 USPQ2d 1258 (Fed. Cir. 1989).

Claims 19-20, 24-27, 29-32, 65-68, 73-74, 90-91, 95-98, 100-102, and 113-116 specify that the saponin be derived from *Quillaja saponaria* and possess immune adjuvant activity. Agrawal teaches the use of saponins as delivery agents. Agrawal does not state the source of saponin or disclose any immune adjuvant activity possessed by the saponins. In fact, Agrawal actually teaches away from, and would provide a disincentive to use, any saponins possessing immune adjuvant activity, since Agrawal's goal is to *decrease* immunogenicity of its administered composition. Thus, Agrawal fails to explicitly disclose every the claim limitation and thus cannot explicitly anticipate the claims.

Because Agrawal fails to explicitly teach each and every limitation of the claims, anticipation can only be shown by inherency - -namely that a "saponin" as disclosed by Agrawal would necessarily be derived from *Quillaja saponaria* and would necessarily possess immune adjuvant activity. However, this is not the case. There are saponins that are not derived from *Quillaja saponaria*, and there are saponins that do not possess immune adjuvant activity, that can form liposome-like structures and act as a delivery vehicle. For example, the saponins alfalfa hederagenin and Quinoa form liposome-like structures called ISCOMS but lack adjuvanticity (Bomford et al., 1992, *Vaccine* 10:572-577, Reference C05 submitted herewith). Thus, Agrawal does not anticipate the rejected claims under the doctrine of inherency.

In view of the foregoing, Applicant requests that the Examiner withdraws the rejections under 35 U.S.C. § 102.

C. Rejections Under 35 U.S.C. § 103

Claims 19-32, 63-69, 70, 73-77, 80-83, 90, 91, 95-98, 100-102. and 113-116 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Weiner et al., 1997, *PNAS* 94:10833-10837 ("Weiner") in view of Kensil, 1996, *Critical Reviews in Therapeutic Drug Carrier Systems* 13:1-55 ("Kensil I"). According to the Examiner, Weiner discloses an immunostimulatory oligonucleotide containing unmethylated CpG dinucleotides with the sequence of SEQ ID NO: 1, but does not disclose the combination of such immunostimulatory oligonucleotides and a saponin. Kensil I teaches the use of the saponin adjuvant QS-21 in combination with tumor antigens to enhance the immune response to said tumor antigen when administered to a subject. The Examiner contends that it would have been obvious to combine the two known adjuvants (the immunostimulatory oligonucleotide containing unmethylated CpGs of SEQ ID NO: 1 and QS-21), particularly in light of a teaching in Weiner that provides an invitation to experiment with combinations of immunostimulatory oligonucleotides with other adjuvants.

In addition, claims 19-27, 63-68, 71-78, 80-83, 90, 91, 95-98, 10-102, and 113-116 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chu et al., 1997, *Journal of Experimental Medicine* 186:1623-1631 ("Chu") in view of Kensil I. According to the Examiner, Chu teaches administering phosphorothioate oligonucleotide 1826 or 1760 as an adjuvant to increase the IgG2a immune response in a mouse. Phosphorothioate oligonucleotide 1826 or 1760 have unmethylated CpG motifs and 1826 is equivalent to SEQ ID NO:2. The Examiner admits that there is no suggestion in Chu, however, to combine the phosphorothioate oligonucleotides with QuilA, QS-7, QS-17, QS-18, or QS-21. According to the Examiner, this deficiency of Chu is remedied by Kensil I, because Kensil I allegedly teaches the combination of Quil A, QS-7, QS-17, QS-18 or QS-21 with other adjuvants to increase the adjuvant effect. Applicant respectfully disagrees.

Assuming, *arguendo*, that the cited references did make a *prima facie* case of obviousness, Applicant has demonstrated the unexpected result of synergism of immunostimulatory oligonucleotides containing unmethylated CpG dinucleotides and saponin adjuvants, thereby rebutting any *prima facie* case of obviousness. The Examiner agrees that Applicant has shown unexpected results with the specific combination of QS-21 and phosphorothioate oligonucleotides 1758 (page 17, lines 14-15 of the Office Action mailed July 26, 2001) and 1826 (page 14, lines 1-2 of the Office Action mailed February 12, 2002). The Examiner, however, questions the generalizablity of these results to the

genus of immunostimulatory oligonucleotides comprising at least one unmethylated CpG dinucleotide and the genus of saponin possessing immune adjuvant activity.

With respect to the genus of immunostimulatory oligonucleotides, Applicant points out that immunostimulatory oligonucleotides comprising at least one unmethylated CpG dinucleotide are generally expected to act in the same manner, and thus share the characteristic of synergism with saponins from *Quillaja saponaria*, since they exert their activity through the same receptor and thus share the same mechanism of action. The cellular response to oligonucleotides containing unmethylated CpG dinucleotides is mediated by a Toll-like receptor, TLR9 (Hemmi et al., 2000, *Nature* 408:740-5, submitted herewith as Reference C01). TLR9-deficient (knockout) mice are unable to respond to oligonucleotides containing unmethylated CpG dinucleotides and thus do not demonstrate increased immunostimulatory effects such as proliferation of splenocytes, increased production of inflammatory cytokines, and increased maturation of dendritic cells (see page 741, second column, line 6 to page 742, first column, line 28 of Hemmi et al., Reference C01). The current model for the mechanism through which unmethylated CpG dinucleotides act to elicit an immunostimulatory response is that TLR9 directly binds the immunostimulatory oligonucleotides containing CpG dinucleotides and becomes endocytosed to then allow activated TLR9 to bind MyD88, IRAK, and TRAF6 which then causes a signaling cascade culminating in transcription of gene products responsible for the immunostimulatory effects seen when immunostimulatory oligonucleotides containing unmethylated CpG dinucleotides are administered (see Figure 1 of Wagner, 2001, *Immunity* 14:499-502, submitted herewith as Reference C04). Thus, the genus of oligonucleotides having unmethylated CpG dinucleotides is expected in general to work through the same mechanism and thus demonstrate the same activity.

Applicant demonstrated in the working examples of the instant specification that oligonucleotides 1758 and 1826 have a synergistic immunostimulatory adjuvant activity in combination with QS-21. Furthermore, Applicant submitted International Publication No. WO 00/62800 ("Friede") in connection with the Amendment filed September 16, 2002 showing that an additional oligonucleotide, 2006[1], has a synergistic immunostimulatory

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[1] Applicant would like to point out that 2006 differs in sequence from 1758 and 1826. On page 16, footnote 1 of the Amendment filed September 16, 2002, Applicant stated that Friede's nomenclature differs from Applicant's and erroneously characterized

adjuvant activity in combination with QS-21. Data concerning the synergism between 2006 and QS-21 was offered to show proof of principle that any oligonucleotide containing at least one unmethylated CpG dinucleotide will synergize with a saponin possessing immune adjuvant activity. It is immaterial that oligonucleotide 2006 was not available at the time of filing, rather what is significant is that synergism was demonstrated in accordance with the teaching of the instant specification. Applicant contends that the salient feature of all three oligonucleotides is unmethylated CpG dinucleotides, which as discussed above, generally share the same mechanism of action, and, as such, any immunostimulatory oligonucleotide comprising at least one unmethylated CpG dinucleotide would be expected to be synergistic when administered in combination with a saponin possessing an immune adjuvant activity that is from *Quillaja saponaria*.

The Examiner further asserts that, although Applicant has demonstrated an unexpected result for QS-21, the genus of all saponin immunostimulatory adjuvants is not adequately represented by one species (*i.e.*, QS-21). The present claims as amended are limited to those saponins that possess immune adjuvant activity *and* are derived from *Quillaja saponaria*. Applicant points out that saponins derived from *Quillaja saponaria* that possess immune adjuvant activity share a common structure, and thus would be expected to function in the same manner with respect to the property of synergism with immunostimulatory oligonucleotides containing unmethylated CpG dinucleotides. For example, QS-7, QS-17, QS-18, and QS-21 are all saponins that are isolated from *Quillaja saponaria*. All are structurally very similar. Kensil et al. (1993, "Novel Adjuvants from *Quillaja saponaria* Molina" in AIDS Research Reviews Volume 3 edited by Koffet al. New York; "Kensil II") shows the structures in Figure 2 of QS-17, QS-18, and QS-21, derived from comparison of monosaccharide composition and molecular weight. Compared to the large portion of the structure that is identical, any differences are minor.

All immunostimulatory adjuvant active *Quillaja saponaria* saponins whose structure is known to Applicant share two structural features - - a triterpene backbone and a 2,3, glucuronic acid carboxyl group (see the paragraph spanning pages 1403 and 1404 of Soltysik et al., 1995, *Vaccine* 13:1404-10, submitted herewith as Reference C03). Modification of the triterpene aldehyde of the backbone inactivated the ability of QS-21 to

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2006 as having the same sequence as the oligonucleotide called 1826 by Applicant. In reality, oligonucleotide 1001 of Friede corresponds to the sequence of Applicant's 1826.

stimulate antibody production and cytolytic T lymphocyte activity (page 1408, second column, first full paragraph of Soltysik et al (Reference C03).

Furthermore, unlike the majority of saponins from species other than *Quillaja saponaria*, all *Quillaja saponaria* saponins are acylated. QS-17, QS-18 and QS-21 are acylated at identical positions and removal of this acyl group decreases immune adjuvant activity as compared to acylated counterparts (see page 2808, paragraph spanning the first and second columns of Liu et al., 2002, *Vaccine* 20:2808-15, submitted herewith as Reference C02). Thus, there are specific structural components that are required for immune adjuvant activity.

Applicant has discovered that adjuvant active saponins derived from *Quillaja saponaria* can be combined with immunostimulatory oligonucleotides for a synergistic effect. Thus, within the genus of saponins encompassed by the claims, which includes for example Quil A, QS-7, QS-17, QS-18, and QS-21, one of ordinary skill in the art would expect each to have a synergistic effect when combined with an immunostimulatory oligonucleotide in light of the data presented in the instant specification. Thus, all of the combinations would be expected to produce adjuvant effects that are greater than simply additive. In fact, the Examiner acknowledges that QS-7, QS-17, QS-18, and QS-21 all have equivalent adjuvant effects (page 14, lines 18-19 of the Office Action mailed July 26, 2001).

Because of the structural similarity of the *Quillaja saponaria* saponins and the correlation of structure with function, the claimed genus is supported by the demonstrated data. The Court of Customs and Patent Appeals stated (In re Kollman, 595 F.2d 48:

> We feel that the unobviousness of a broader claimed range can, in certain instances, be proven by a narrower range of data. Often, one having ordinary skill in the art may be able to ascertain a trend in the exemplified data which would allow him to reasonably extend the probative value thereof. The proof, thus considered, might then be sufficient to rebut a PTO holding of prima facie obviousness.

In view of the foregoing, Applicant respectfully requests that the Examiner withdraws the rejections under 35 U.S.C. § 103.

CONCLUSION

Applicant respectfully requests that the amendments and remarks made herein be entered and made of record in the file history of the present application. Withdrawal of the Examiner's rejections and a notice of allowance are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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